CLAIMS

What is claimed is:

1. A genetically-modified, non-human mammal comprising an α2/δ1 gene comprising an 290-like mutation.

2. A genetically-modified, non-human mammal, wherein the modification results in a mutated α2/δ2 gene encoding a polypeptide selected from the group consisting of:

   a) An α2/δ2 polypeptide comprising an arginine to non-arginine substitution in at least one of the two flanking arginines in an RRR motif unique to said polypeptide;

   b) An α2/δ2 polypeptide comprising an arginine to aliphatic amino acid substitution in at least one of the two flanking arginines in an RRR motif unique to said polypeptide;

   c) An α2/δ2 polypeptide comprising an arginine to alanine substitution in at least one of the two flanking arginines in an RRR motif unique to said polypeptide;

   d) An α2/δ2 polypeptide comprising a deletion of at least one of the flanking arginines in an RRR motif unique to said polypeptide;

   e) An α2/δ2 polypeptide comprising a deletion of up to 9 residues immediately N-terminal to an RRR motif unique to said polypeptide, a deletion of up to 5 residues immediately C-terminal to an RRR motif unique, and a deletion of at least one of the flanking arginines in an RRR motif unique to said polypeptide;

   f) An α2/δ2 polypeptide comprising a deletion of up to of up to 9 residues immediately N-terminal to an RRR motif unique to said polypeptide, and a deletion of at least one of the flanking arginines in an RRR motif unique to said polypeptide;

g) An α2/δ2 polypeptide comprising a deletion of up to 5 residues immediately C-terminal to an RRR motif unique, and a deletion of at least one of the flanking arginines in an RRR motif unique to said polypeptide; and

h) An α2/δ2 polypeptide according to a)-g) having at least one conservative amino acid substitution at a position other than a flanking arginines in said RRR motif.

3. A genetically-modified, non-human mammal, wherein the modification results in a mutated α2/δ2 gene encoding a polypeptide selected from the group consisting of:

a) An α2/δ2 polypeptide that is identical to a wildtype α2/δ2 polypeptide except that it has an arginine to non-arginine substitution in at least one of the two flanking arginines in an RRR motif unique to said polypeptide;

b) An α2/δ2 polypeptide that is identical to a wildtype α2/δ2 polypeptide except that it has an arginine to aliphatic amino acid substitution in at least one of the two flanking arginines in an RRR motif unique to said polypeptide;

c) An α2/δ2 polypeptide that is identical to a wildtype α2/δ2 polypeptide except that it has an arginine to alanine substitution in at least one of the two flanking arginines in an RRR motif unique to said polypeptide;

d) An α2/δ2 polypeptide that is identical to a wildtype α2/δ2 polypeptide except that it has a deletion of at least one of the flanking arginines in an RRR motif unique to said polypeptide;

e) An α2/δ2 polypeptide that is identical to a wildtype α2/δ2 polypeptide except that it has a deletion of up to 9 residues immediately N-terminal to an RRR motif unique to said polypeptide, a deletion of up to 5 residues immediately C-terminal to an RRR motif unique, and a deletion of at least one

of the flanking arginines in an RRR motif unique to said polypeptide;

f) An α2/δ2 polypeptide that is identical to a wildtype α2/δ2 polypeptide except that it has a deletion of up to of up to 9 residues immediately N-terminal to an RRR motif unique to said polypeptide, and a deletion of at least one of the flanking arginines in an RRR motif unique to said polypeptide;

g) An α2/δ2 polypeptide that is identical to a wildtype α2/δ2 polypeptide except that it has a deletion of up to 5 residues immediately C-terminal to an RRR motif unique, and a deletion of at least one of the flanking arginines in an RRR motif unique to said polypeptide; and

h) An α2/δ2 polypeptide according to a)-g) having at least one conservative amino acid substitution at a position other than a flanking arginine in said RRR motif.

4. The genetically modified, non-human mammal of claim 3 wherein said wildtype α2/δ2 polypeptide is set forth in SEQ ID NO: 32, 33, 34, 35, or 36.

5. A genetically-modified, non-human mammal, wherein the modification results in a mutated α2/δ2 gene encoding a polypeptide selected from the group consisting of:

a) An α2/δ2 polypeptide that is identical to a wildtype α2/δ2 polypeptide except that it has an amino acid other than arginine at position 288, 290 or both;

b) An α2/δ2 polypeptide that is identical to a wildtype α2/δ2 polypeptide except that it has an aliphatic amino acid at position 288, 290 or both;

c) An α2/δ2 polypeptide that is identical to a wildtype α2/δ2 polypeptide except that it has an alanine at position 288, 290 or both;

d) An α2/δ2 polypeptide that is identical to a wildtype α2/δ2 polypeptide except that it has a lysine at position 288, 290 or both; and

e) The wildtype mammalian α2/δ2 polypeptide according to A)-d) having at least one conservative amino acid substitution at a position other than residue 288 and 290.

6. The mammal of claim 2, wherein said mammal exhibits at least one phenotypic characteristic selected from the group consisting of:

a) the phenotypic characteristic of reduced α2/δ ligand binding to central nervous system of said mammal;

b) the phenotypic characteristic of reduced gabapentin binding to central nervous system of said mammal;

c) the phenotypic characteristic of reduced analgesic efficacy of an α2/δ ligand in said mammal;

d) the phenotypic characteristic of reduced analgesic efficacy of pregabalin in said mammal;

e) the phenotypic characteristic of reduced sedative efficacy of an α2/δ ligand in said mammal wherein said mammal is subjected to a sedation test;

f) the phenotypic characteristic of reduced anticonvulsant efficacy of an α2/δ ligand in said mammal wherein said mammal is subjected to a sedation test; and

g) the phenotypic characteristic of reduced anxiolytic efficacy of an α2/δ ligand in said mammal wherein said mammal is subjected to a sedation test.

7. The mammal of claim 2, wherein said mammal is a rodent.

8. The rodent of claim 7, wherein said rodent is a mouse.

9. The non-human mammal of claim 2, wherein said mammal is homozygous for said modification.

10. An isolated nucleic acid molecule having a sequence encoding a polypeptide comprising the sequence set forth in SEQ ID NO: 39.

11. An isolated nucleic acid molecule comprising a nucleotide sequence set forth in SEQ ID NO: 40.

12. A genetically-modified, non-human mammal comprising the nucleic acid sequence of claim 10.

13. A targeting vector for producing a transgenic animal, said vector comprising a nucleic acid having a nucleotide sequence encoding a polypeptide according to claim 2.

14. A host cell comprising the vector of claim 13.

15. A non-human mammal that is the progeny of a first mammal and second mammal wherein the first mammal is a genetically-modified, non-human mammal, according to claim 2; and the second mammal is a genetically-modified, non-human mammal wherein the modification results in a mutated α2/δ1 gene encoding a polypeptide selected from the group consisting of:

a) An α2/δ1 polypeptide comprising an arginine to non-arginine substitution in at least one of the two flanking arginines in an RRR motif unique to said polypeptide;

b) An α2/δ1 polypeptide comprising an arginine to aliphatic amino acid substitution in at least one of the two flanking arginines in an RRR motif unique to said polypeptide;

c) An α2/δ1 polypeptide comprising an arginine to alanine substitution in at least one of the two flanking arginines in an RRR motif unique to said polypeptide;

d) An α2/δ1 polypeptide comprising a deletion of at least one of the flanking arginines in an RRR motif unique to said polypeptide;

e) An α2/δ1 polypeptide comprising a deletion of up to 9 residues immediately N-terminal to an RRR motif unique to said polypeptide, a deletion of up to 5 residues immediately C-terminal to an RRR motif unique, and a deletion of at least one of the flanking arginines in an RRR motif unique to said polypeptide;

f) An α2/δ1 polypeptide comprising a deletion of up to of up to 9 residues immediately N-terminal to an RRR motif unique to said polypeptide, and a deletion of at least one of the flanking arginines in an RRR motif unique to said polypeptide;

g) An α2/δ1 polypeptide comprising a deletion of up to 5 residues immediately C-terminal to an RRR motif unique, and a deletion of at least one of the flanking arginines in an RRR motif unique to said polypeptide; and

h) An α2/δ1 polypeptide according to a)-g) having at least one conservative amino acid substitution at a position other than a flanking arginines in said RRR motif.

16. The mammal of claim 15 wherein said mammal exhibits reduced gabapentin binding to its central nervous system in comparison to said first mammal or in comparison to said second mammal.

17. A genetically-modified animal cell, wherein the modification comprises a mutated gene encoding a polypeptide according to claim 2.

18. The animal cell of claim 17, wherein said cell is an embryonic stem (ES) cell or an ES-like cell.

19. The animal cell of claim 17, wherein said cell is isolated from a genetically-modified, non-human mammal containing a modification that results in a mutated gene.

20. The animal cell of claim 19, wherein said cell is an embryonic fibroblast, stem cell, neuron, skeletal or cardiac muscle cell, myoblast, brown or white adipocyte, hepatocyte, or pancreatic β cell.

21. The animal cell of claim 17, wherein said cell is murine.

22. The animal cell of claim 17, wherein said cell is human.

23. The animal cell of claim 17, wherein said cell is homozygous for said modification.

24. A method of identifying a gene that demonstrates modified expression as a result of reduced α2/δ2 activity in an animal cell, said method comprising assessing the expression profile of an animal cell containing a genetic modification that disrupts an α2/δ2 gene, and comparing said profile to that from a wildtype cell.

25. The method of claim 24, wherein said cell is homozygous for a genetic modification that disrupts the α2/δ2 gene.

26. A method of identifying a protein that demonstrates modified expression or post-translational modification as a result of reduced α2/δ2 activity in an animal cell, said method comprising assessing the proteomic profile of an animal cell containing a genetic modification that disrupts a α2/δ2 gene, and comparing said profile to that from a wildtype cell.

27. A method of claim 26, wherein said cell is homozygous for a genetic modification that disrupts the α2/δ2 gene.

28. A method for producing a transgenic animal having a modified response in an α2/δ1-, or α2/δ2, or α2/δ1 and α2/δ2-mediated disorder or activity relative to a wildtype animal, said method comprising:

a) transfecting ES cells with a targeting vector for producing a transgenic animal, said vector comprising a nucleic acid having a nucleotide sequence encoding a polypeptide according to claim 2;

b) selecting transfected cells undergone homologous recombination;

c) implanting said selected transfected cells into blastocysts;

d) producing transgenic animals from said blastocysts.

29. The method of claim 28, wherein said activity or disorder of claim 28 is selected from pain, hyperalgesia, anxiety, sedation, epilepsy, convulsion.

30. A method for determining whether the physiological effect of a compound on a disorder or activity involves α2/δ2 subunit polypeptide residues that mediate the physiological effect of an α2/δ ligand, said method comprising

a) providing a first group of mammals according to claim 2 and a second group of corresponding wildtype mammals,

b) treating a first subset of each said group with an α2/δ ligand,

c) treating a second subset of each said group with a test compound,

d) testing each subset for an activity or disorder associated with α2/δ1 or α2/δ2, and

e) comparing the response of each said each said groups and subsets.

31. The method of claim 30 wherein said activity or disorder of is selected from pain, hyperalgesia, anxiety, sedation, epilepsy, convulsion.

32. The method of claim 30 wherein said α2/δ ligand is gabapentin.

33. The method of claim 30 wherein said α2/δ ligand is pregabalin.

34. A method for identifying compounds that exert their physiological effect on a disorder or activity through an α2/δ2 subunit polypeptide, said method comprising

a) providing a first group of mammals according to claim 2 and a second group of corresponding wildtype mammals,

b) treating each said group with a test compound,

c) testing each group for an activity or disorder associated with α2/δ1, and

d) comparing the response of each said each said groups.

35. A method for identifying compounds that exert their physiological effect on a disorder or activity through an α2/δ2 subunit polypeptide, said method comprising

a) providing a first group of mammals according to claim 2 and a second group of corresponding wildtype mammals,

b) treating a first subset of each said group with a ligand that binds an α2/δ subunit polypeptide ,

c) treating a second subset of each said group with a test compound,

d) testing each subset for an activity or disorder associated with α2/δ1 or α2/δ2, and

e) comparing the response of each said each said groups and subsets.

36. The method of claim 35 wherein said ligand is gabapentin.

37. The method of claim 35 wherein said activity or disorder is selected from pain, hyperalgesia, anxiety, sedation, epilepsy, convulsion.

38. A method for determining a role of α2/δ2 polypeptide in an activity or disorder, said method comprising

a) providing a first group of mammals according to claim 2 and a second group of corresponding wildtype mammals,

b) subjecting each said group to a procedure indicative of an activity or disorder, and

c) comparing the response of each said group.

39. The method of claim 38 wherein said activity or disorder of is selected from pain, hyperalgesia, anxiety, sedation, epilepsy, convulsion.

40. The method of claim 38 wherein said procedure is selected from $\alpha 2/\delta$ ligand binding, gabapentin binding, formalin foot-pad procedure, Tail suspension test, Maximal electro-shock, and Vogel procedure.